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Original Contribution

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Prevalence of Lysosomal Storage Disorders

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ABSTRACT

Context Lysosomal storage disorders represent a group of at least 41 genetically distinct, biochemically related, inherited diseases. Individually, these disorders are considered rare, although high prevalence values have been reported in some populations. These disorders are devastating for individuals and their families and result in considerable use of resources from health care systems; however, the magnitude of the problem is not well defined. To date, no comprehensive study has been performed on the prevalence of these disorders as a group.

Objective To determine the prevalence of lysosomal storage disorders individually and as a group in the Australian population.

Design Retrospective case studies.

Setting Australia, from January 1, 1980, through December 31, 1996.

Main Outcome Measure Enzymatic diagnosis of a lysosomal storage disorder.

Results Twenty-seven different lysosomal storage disorders were diagnosed in 545 individuals. prevalence ranged from 1 per 57,000 live births for Gaucher disease to 1 per 4.2 million live birt sialidosis. Eighteen of 27 disorders had more than 10 diagnosed cases. As a group of disorders, combined prevalence was 1 per 7700 live births. There was no significant increase in the rate of clinical diagnoses or prenatal diagnoses of lysosomal storage disorders during the study period.

Conclusions Individually, lysosomal storage disorders are rare genetic diseases. However, as a they are relatively common and represent an important health problem in Australia.

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Lysosomal storage disorders (LSDs) represent a group of at least 41 distinct genetic diseases, each one resulting from a deficiency of a particular lysosomal protein or, in a few cases, from nonlysosomal proteins, that are involved in lysosomal biogenesis. Most LSDs are inherited in an autosomal recessive manner, with the exception of Fabry disease and mucopolysaccharidosis (MPS) type II, which show X-linked recessive inheritance.

The number of LSDs is steadily increasing as new disorders are characterized biochemically and genetically. A deficiency of cathepsin K has recently been described that results in an LSD called *pyknodysostosis*.[1] In the last 2 years, infantile neuronal ceroid lipofuscinosis (NCL), also known disease, has been shown to result from a deficiency of palmityl protein thioesterase,[2-3] and class infantile NCL has been shown to result from a deficiency of a carboxypeptidase.[4] Many LSDs hav classified into clinical subtypes (such as the Hurler-Scheie definition of MPS type I or the infantil juvenile-, and adult-onset forms of Pompe disease), but it is clear that most LSDs have a broad of clinical severity and age of presentation.

With the advent of molecular biology and the characterization of many of the LSD genes, it is nc recognized that the range of severity may in part be ascribed to different mutations within the s However, genotype-phenotype correlations do not always hold. In Gaucher disease, for example sometimes substantial differences in the clinical manifestation of the disease between siblings ar some instances, one sibling is severely affected while another is virtually free of disease.[5] Other including genetic background and environmental factors, presumably play a role in disease prog

Although each LSD results from mutations in a different gene and consequent deficiency of enzy activity or protein function, all LSDs share a common biochemical characteristic in that the disor in an accumulation of normally degraded substrates within lysosomes. The particular substrates and the site(s) of storage vary, although the substrate type is used to group LSDs into broad cat including MPSs, lipidoses, glycogenoses, and oligosaccharidoses.[6] These categories show many similarities within groups as well as significant similarities between groups. Common features of LSDs include bone abnormalities, organomegaly, central nervous system dysfunction, and coars facies.

There have been a number of reports on the prevalence of particular disorders in select populati note is the level of Gaucher disease and Tay-Sachs disease in the Ashkenazi Jewish population, to be 1 per 855 and 1 per 3900, respectively.[5, 7] Prevalences as high as 1 per 18,500 for aspartylglycosaminuria in the Finnish population[8] and 1 per 24,000 for MPS type III in the Nethe have also been reported. In addition, there have been a number of limited studies on the preval some LSDs in different countries.[10-15] However, in general, these studies have not been comprel and have not covered all LSDs. As the development of therapies for this group of disorders proc the possibilities for neonatal screening are explored, it becomes important to obtain accurate val prevalence of the disorders. These data will be required to accurately assess the cost of these di public health care systems and will be a key factor in the adoption of screening and treatment p for LSDs.

In this article, we present a summary of all LSD diagnoses in Australia for the period 1980 throu

METHODS

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In this study, patients diagnosed as having an LSD have a reduced level of 1 or more lysosomal proteins, which leads to the storage of substrate within their lysosomes and results in the development of clinical problems and a subsequent reduction in their quality of life.

Retrospective data on the enzymatic diagnosis of LSDs, both from patient referrals and prenatal diagnoses for the period January 1, 1980, through December 31, 1996, were collec the National Referral Laboratory, Department of Chemical Pathology, Women's and Children's H Adelaide, Australia, and from the Division of Chemical Pathology, Royal Brisbane Hospitals, Brist Australia. All diagnoses were performed at these 2 centers and this represents all enzymatic ana performed in Australia during this period. No data were collected on the diagnosis of pyknodysos glycogen-storage disease type II-B, or the various forms of Batten disease, which are currently i diagnosed enzymatically in Australia.

Data on the number of births in Australia were collected from the Australian Bureau of Statistics (Canberra). Data were compiled according to disorder, year of diagnosis, and age of patient (inc prenatal diagnoses), and correlated with Australian birth rates for each year. Instances in which were 2 or more affected siblings were identified.

Incidence rates were calculated by dividing the number of postnatal diagnoses by the number of during the study period. Prevalence rates were calculated by dividing the number of postnatal pl prenatal diagnoses by the number of births during the study period. The total number with pren diagnoses who were not live-born were not included in the denominator because this figure was accurately known and would not have made a significant difference to the prevalence figures. Ca frequency was calculated by dividing the prevalence value by 4 and finding the square root. Carı frequency for X-linked disorders was equal to the prevalence values because the incidence of ca should equal the prevalence of affected births for these disorders.

RESULTS

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For the period January 1980 through December 1996, there were 470 LSD-affected individuals diagnosed in the Australian population. In addition, there were 75 positive LSD prenatal diagnoses for affected fetuses, yielding a total of 545 diagnoses (Table 1). There was no significant increase in the rate of either clinical diagnoses or prenatal diagnoses during the study period (Figure 1). These diagnoses represent 27 different LSDs, whereas there were 10 LSDs for which there were no diagnoses in Australia during this period (Table 2). The prevalence of these disorc ranged from 1 per 57,000 for Gaucher disease to 1 per 4.2 million for sialidosis. The prevalence as a group was calculated to be 1 per 7700 live births. When prenatal diagnoses were not consic incidence for LSDs was 1 per 9000 live births. Mucopolysaccharidosis, a particularly well-defined of LSDs, had a combined prevalence of 1 per 22,500 and represented 35% of all LSDs. Carrier fi were calculated from the prevalence values and ranged from 1 per 119 for Gaucher disease to 1 for sialidosis (Table 1). Comparison of the number of LSD diagnoses in the different states of Au (Table 3) indicates similar prevalence values in all major population centers. The exceptions, Au: Capital Territory, Northern Territory, and Tasmania, are all low-population areas that use genetic in neighboring states and, as such, would have had some patients recorded in those states.

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Table 1. Diagnosis of Lysosomal Storage Disorders in Australia*

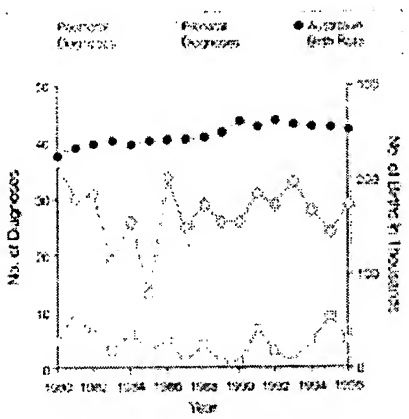

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Figure. Postnatal and Prenatal Lysosomal Storage Disord
Diagnoses Made in Australia From 1980 Through 1996

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Table 2. Disorders Not Detected Enzymatically in the Australian Populatio

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Table 3. Prevalence of Lysosomal Storage Disorders by State

We determined the median age of the patients at diagnosis for each LSD and report these togetl the low and high values for each disorder (Table 4). Although for some disorders, the number of was not high enough to make these data statistically significant, it still gives an indication of the ages at which these disorders can present. Most disorders (18/27) had more than 10 diagnoses period. These data demonstrate that certain disorders, in particular Fabry disease, can present r late in life, with a mean age at diagnosis of 28.6 years, although for some individuals diagnosis in the first year of life. Clinicians should note the wide range of the clinical spectrum presenting i disorders. In some LSDs, including Krabbe disease, MPS type I, Pompe disease, and Sandhoff di median age at diagnosis was younger than 1 year, although the range of ages in each disorder s reflected a considerable variation in the clinical spectrum.

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Table 4. Age at Diagnosis of Patients With Lysosomal Storage Disorders*

Of the 470 clinical diagnoses, there were 79 individuals who had 1 or more affected siblings. The families with twins, 9 families with an index case who in full knowledge had 1 or more additional children, and 26 families who had had 2 affected children before the first had an LSD diagnosed.

these 26 families, the affected individuals were adults (older than 18 years) when the disease w diagnosed.

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The prevalence values for individual LSDs clearly define these as rare genetic disorders. Gaucher disease was the most common, with a prevalence of 1 per 57,000 births. However, when taken as a group, LSDs are far more common, with a prevalence of 1 per 7700 births. Each year in Australia there are, on average, 28 LSD diagnoses made, with an additional 4 to 5 prenatal diagnoses. Although exact national figures for the number of MPS referrals are unavailable, in South Australia, 150 to 250 urine screening tests for MPS are performed each year to diagnose MPS, on average patient. White-cell enzymology, which is performed for most other LSDs, is performed on 400 tc patients per year nationally, resulting in an average of 18 diagnoses. These estimates suggest considerable overlap between clinical features of LSDs and other conditions, but may also indica presence of additional as yet undefined LSDs. Although prenatal diagnosis is possible for most L practical prenatal screening tests are available for any LSD.

The life expectancy of a patient with an LSD depends on the particular disorder, the severity, an treatment available. In MPS, this can range from lethal fetal hydrops to an almost-normal life expectancy.[16] In most, if not all, disorders, there is a strong correlation among age at diagnosis and life expectancy. The difference between the median age (2.7 years) and average age (9.7 y diagnosis of an LSD in Australia reflects the relatively few adult patients who have an almost-no expectancy. Based on the average age at diagnosis of 9.7 years and an average of 28 affected i born each year, we estimate that there are currently about 270 individuals with an undiagnosed possibly up to twice that number of patients with a diagnosed LSD in Australia.

That there were only 2 centers involved in the enzymatic diagnosis of LSDs greatly facilitated th collection of data for this study; as a consequence, we have a high level of confidence that few c were missed. Our confidence is supported by the state-by-state breakdown of the prevalence va the LSDs, with the 5 major population centers showing similar prevalence data. Had 1 or more s missed a significant number of cases, this would present as uneven prevalence values among st addition, there was no significant variation in the number of diagnoses made per year during the period; this would suggest that the patient identification rate is constant and close to 100% for t disorders. It is possible, however, that there are some individuals at the less-severe end of the c spectrum of some disorders, particularly in the adult population, in whom an LSD was not diagn Gaucher disease is likely in this group. Similarly, we observed that there was no increase in the prenatal diagnoses for the period of the study; this again reflects the steady rate of diagnosis of disorders.

To calculate incidence, prevalence, and carrier frequency values, we needed to make certain ass We assumed that the rate of postnatal diagnosis was equivalent to the birth rate for each disord postnatal diagnosis was less than the birth rate, as a result of undiagnosed early death, then ou estimates of incidence values would be low. This is unlikely because all unexpected child deaths Australia result in postmortem examinations, including histopathology studies. We also assumed parents of affected individuals were heterozygous for the disorders (with the exception of X-link disorders). If this were not the case, then our estimates of carrier frequency would be low; howe homozygous parents, in what are predominantly childhood disorders, are not common and, as s have little effect on our carrier frequency estimates.

The Australian population is predominantly of British extraction, with a significant contribution fr European countries and, to a lesser extent, Asian countries. As such, this population would be cc with that of most Anglo-Celtic countries. Therefore, these results could be extrapolated to the w Hispanic populations in the United States, Canada, and the United Kingdom. However, a higher of Ashkenazi Jews in a community may increase the prevalence of Gaucher disease and Tay-Sac disease.

Although no data are available on the ethnic background of those diagnosed as having an LSD, v evidence that the Ashkenazi Jewish population contributed significantly to the figures for either (disease or Tay-Sachs disease in Australia. The Ashkenazi Jewish population in Australia is estim 105,000 and is concentrated in Victoria and New South Wales. Despite this, we see no increase prevalence of either Gaucher disease or Tay-Sachs disease in these states compared with other Australia. This may be the result of outbreeding from the Jewish community into the general po screening program for the detection of Tay-Sachs disease carriers in the Jewish community was commenced in 1994; however, this would have had only a minimal effect on this study, which c period 1980 to 1996.

The cost to the community, in particular the health care system, of individuals with LSDs is signi have calculated the medical costs for a patient with severe MPS I who has not had a bone marro transplant to be approximately Aust $80,000 (US $56,000) per year, based on hospital admissic hospital procedures, and outpatient visits during a 2.5-year period. In addition, such a patient w require full-time nursing home care while attending a special school, further increasing the cost community. Bone marrow transplantation costs, on average, Aust $41,000 (US $29,000). Enzyn replacement therapy for Gaucher disease currently costs between Aust $140,000 and $250,000 $98,000-$175,000) per year, although the cost for enzyme replacement therapy should decreas efficient enzyme production systems are developed. Given that some of the affected individuals less-severe end of the clinical spectrum, the total cost to the community for individuals with an I Australia is thought to be in the tens of millions of dollars per year. Although it is useful to deter cost of these disorders to the community, in particular to the health care system, this represent fraction of the real cost, in human terms, of these disorders.

There were 39 families with more than 1 affected child; this highlights the need for early diagno these disorders because in most cases, there were 2 affected children born before the first was (as having an LSD. Early detection of LSDs, such as that possible in the neonatal screening progr phenylketonuria and other genetic diseases, would provide the option for prenatal diagnosis for more families carrying these disorders. In addition, early detection would maximize the efficacy and proposed therapies for LSDs. The efficacy of these therapies, particularly for those LSDs inv central nervous system and bone pathologies, will rely heavily on the early diagnosis and treatm disorder, before the onset of irreversible disease. A further consideration, critical to bone marrov transplant therapy, is that early diagnosis of the LSD will allow clinicians to take advantage of th of opportunity presented by the naturally suppressed immune system of the neonate to maximi chances of a successful engraftment. Early intervention has the potential to reduce costs associa LSDs. Studies into the development of neonate screening for LSDs are currently in progress.[17]

Recently, there have been several advances made in the understanding of NCLs, a group of at le disorders classified by age at onset. Previously, these disorders were diagnosed histopathologic than enzymatically and, consequently, we have no incidence data available. However, NCLs are common: estimates of incidence levels range from a global incidence for all forms of 1 per 12,5C per 78,000 for all forms in Germany.[19] In Finland, where there is a particularly high level, incide of 1 per 13,000 for infantile and 1 per 21,000 for juvenile forms have been reported.[20] Clearly, I

going to contribute importantly to the overall prevalence of LSDs. A rate of 1 per 50,000 births f would alter the prevalence of LSDs from 1 per 7700 to 1 per 6700. Further epidemiological studi required for this group of disorders.

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1. Gelb BD, Shi GP, Chapman HA, Desnick RJ. Pyknodysostosis, a lysosomal disease caused by cathepsin K deficiency. *Science.* 1996;273:1236-1238. ABSTRACT

2. Vesa J, Hellsten E, Verkruyse LA, et al. Mutations in the palmityl protein thioesterase gene causing infantile neuronal ceroid lipofuscinosis. *Nature.* 1995;376:584-587. CrossRef | ISI | MEDLINE

3. Hellsten E, Vesa J, Olkkonen VM, Jalanko A, Peltonen L. Human palmityl protein thioesterase: evidence for lysosomal targeting of the enzyme and disturbed cellular routing in infantile neuronal ceroid lipofuscinosis. *EMBO J.* 1996;15:5240-5245. ABSTRACT

4. Sleat DE, Donnelly RJ, Lackland H, et al. Association of mutations in a lysosomal protein with late-infantile neuronal ceroid lipofuscinosis. *Science.* 1997;277:1802-1805. ABSTRACT/FULL TEXT

5. Beutler E, Grabowski GA. Gaucher disease. In: Scriver CR, Beaudet AC, Sly WS, Valle D, eds. *Metabolic and Molecular Basis of Inherited Disease.* Vol 2. 7th ed. New York, NY: McGraw-Hill Bc 1995:2641-2670.

6. Hopwood JJ, Brooks DA. An introduction to the basic science and biology of the lysosome and diseases. In: Applegarth DA, Dimmick JE, Hall JG, eds. *Organelle Diseases.* New York, NY: Chap Hall; 1997:7-35.

7. Petersen GM, Rotter JI, Cantor RM, et al. The Tay-Sachs disease gene in North American Jew populations: geographic variations and origin. *Am J Hum Genet.* 1983;35:1258-1269. ISI | MEDLI

8. Arvio M, Autio S, Louhiala P. Early clinical symptoms and incidence of aspartylglycosaminuria *Acta Paediatr.* 1993;82:587-589. ISI | MEDLINE

9. van de Kamp JJ, Niermeijer MF, von Figura K, Giesberts MA. Genetic heterogeneity and clinic variability in the Sanfilippo syndrome (types A, B, and C). *Clin Genet.* 1981;20:152-160. ISI | ME

10. Lowry RB, Applegarth DA, Toone JR, MacDonald E, Thunem NY. An update on the frequency mucopolysaccharide syndromes in British Columbia. *Hum Genet.* 1990;85:389-390. ISI | MEDLINE

11. Ozand PT, Gascon G, al Aqeel A, Roberts G, Dhalla M, Subramanyam SB. Prevalence of diffe of lysosomal storage diseases in Saudi Arabia. *J Inherit Metab Dis.* 1990;13:849-861. ISI | MEDLI

12. Krasnopolskaya KD, Mirenburg TV, Aronovich EL, et al. Diagnosis and prevention of lysosom diseases in Russia [published erratum appears in *J Inherit Metab Dis.* 1994;17:111]. *J Inherit M* 1993;16:994-1002. ISI | MEDLINE

13. Czartoryska B, Tylki Szymanska A, Gorska D, Sawnor Korszynska D. Lipidoses detected in P through 1993. *Pediatr Neurol.* 1994;11:295-297. CrossRef | ISI | MEDLINE

14. Michelakakis H, Dimitriou E, Tsagaraki S, Giouroukos S, Schulpis K, Bartsocas CS. Lysosoma diseases in Greece. *Genet Couns.* 1995;6:43-47. MEDLINE

15. Coelho JC, Wajner M, Burin MG, Vargas CR. Selective screening of 10,000 high-risk Braziliar for the detection of inborn errors of metabolism. *Eur J Pediatr.* 1997;156:650-654. CrossRef | ISI |

16. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Scriver CR, Beaudet AC, Sly WS, Va *The Metabolic and Molecular Basis of Inherited Disease.* Vol 2. 7th ed. New York, NY: McGraw-H Co; 1995:2465-2494.

17. Meikle PJ, Brooks DA, Ravenscroft EM, et al. Diagnosis of lysosomal storage disorders: evalu lysosome-associated membrane protein LAMP-1 as a diagnostic marker. *Clin Chem.* 1997;43:13 ABSTRACT/FULL TEXT

18. Rider JA, Rider DL. Batten disease: past, present, and future. *Am J Med Genet Suppl.* 1988; MEDLINE

19. Claussen M, Heim P, Knispel J, Goebel HH, Kohlschutter A. Incidence of neuronal ceroid-lipo in West Germany: variation of a method for studying autosomal recessive disorders. *Am J Med* (1992;42:536-538. ISI | MEDLINE

20. Santavuori P. Neuronal ceroid-lipofuscinoses in childhood. *Brain Dev.* 1988;10:80-83. ISI | M

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